

REMARKS

Claims 85 and 86 are currently canceled without prejudice or disclaimer to pursuing the canceled subject matter in a divisional or continuation application. As a result of this Amendment, claims 83, 84 and 87 are currently pending.

Claims 83 and 84 are presently amended so as to even more clearly describe the claimed invention. Support for the phrase “for two or more molecular markers” as added to claim 83 can be found throughout the specification as filed. See, for example, page 16, line 8 (“two or more molecular markers”) as well as originally filed claim 1 (“two or more molecular markers”). Support for the phrase “one or more of” as added to claim 84 can be found throughout the specification as filed. See, for example, page 16, line 5 (“one or more different types of cells, tissues, organs or *in vitro* assays”) as well as originally filed claim 1 (“one or more different types of cells, tissues organs or *in vitro* assays”).

The Final Office Action dated February 24, 2004 has been carefully reviewed and the following remarks are made in response thereto. In view of these remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 83-87 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As regards claim 83, steps b(ii) and c(ii), the Office Action states that the phrase “storing the array of expression... into a Standardized HBR array” allegedly causes the claims to be vague and indefinite because according to the Examiner it is unclear whether this phrase refers to “a solid substrate or digital representation of the data produced from an HBR array”. However, a claim is not indefinite if, when read in light of the specification, it reasonably apprises those skilled in the art of the scope of the invention. See, for example, *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1378, 55 UPQ2d 1279, 1282, (Fed. Cir. 2000). The definition for ‘Herbal BioResponse [HBR] Array’ is clearly and unambiguously set forth in the as-filed specification at page 18, line 21 to page 19, line 4, as constituting “a data set of two or more observations or

measurements associated with an herbal composition”. Furthermore, this cited section of the specification further states that the Array “may include qualitative and quantitative data” and that such data “can be statistically analyzed in either 2- or 3-dimensional space”. Even more on point to this rejection, a ‘Standardized HBR Array’ is clearly defined therein as “arrays of data associated with a standardized herbal composition” (page 19, line 3-4, underlining added). Thus, one skilled in the art upon referencing the definition of “Standardized HRB Array” as provided in the as-filed specification is fully and unambiguously apprised of the scope of the claimed invention. The Examiner is respectfully requested to withdraw this rejection as the claim is not vague and indefinite when read in light of the specification.

In an effort to advance prosecution, claim 85 has been canceled without prejudice or disclaimer to the inclusion of the subject matter in any later-filed divisional or continuing patent application. Therefore, this rejection as it applies to claim 85 is moot.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 85 and 86 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

In an effort to advance prosecution and without agreeing to the rejection, claims 85 and 86 have been canceled without prejudice or disclaimer to the inclusion of the subject matter in any later-filed divisional or continuing patent application. Therefore, this rejection of claims 85 and 86 is moot.

Rejections under 35 U.S.C. § 103(a)

Claims 83-87 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Khwaja *et al.* (U.S. Patent No. 6,113,907) taken with Schena *et al.* (1996). The rejection will be addressed in as much as it applies to currently pending claims 83, 84 and 87.

Khwaja *et al.* disclose a method for using compositional and bioactivity fingerprints in processing St. John’s Wort to produce pharmaceutical grade compositions. Khwaja *et al.* do not disclose using gene expression profiles in a quality control method for assessing the equivalency of a test batch of an herbal composition to a standardized batch of the same or substantially same

herbal composition, as claimed in the instant invention. In fact, this reference fails to even discuss gene expression.

Schena *et al.* teach using microarrays to examine the physiological response of cultured human T (Jurkat) cells under control, heat-treated and phorbol ester treatment. Schena *et al.* disclose comparing the cellular effects of a single chemical (i.e., phorbol ester) to a control cell. According to the authors, the purpose of the study was to demonstrate that “parallel gene analysis with microarrays provides a rapid and efficient method for large-scale human gene discovery” (Abstract). This reference fails to discuss using gene expression profiles in a quality control method for assessing the equivalency of a test batch of an herbal composition to a standardized batch of the same or substantially same herbal composition.

The Examiner states the following as justification for combining these two very different teachings so as to arrive at the currently-claimed invention (Final Office Action, page 6, paragraph 25):

“An artisan of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement suggested by Khwaja et al. to use bioactivity profiles from microarrays for the quality control process of manufacturing predictable and consistent treatment for patients from plants. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use bioactivity profiles from microarrays for the quality control process of manufacturing predictable and consistent treatment for patients from plants as taught by Khwaja et al. and Schena et al.”

Attached please find a ‘Declaration Under 37 C.F.R. § 1.132’ executed by Dan Theodorescu, M.D., Ph.D., as well as his Curriculum Vitae (CV) as Exhibit A to the Declaration. As demonstrated by his Declaration and CV, Dr. Theodorescu is a person of ordinary skill in the art of botanical/herbal compositions, their use in medicine and their standardization. As set forth in the Declaration, Dr. Theodorescu has reviewed the patent application under consideration, including the presently pending claims, as well as the Final Office Action and the two references cited by the Examiner therein.

In paragraph 5 of his Declaration, Dr. Theodorescu discusses the long-felt need for a method utilizing gene expression profiles for the standardization of herbal compositions and the problem to be solved by such a method. In this same paragraph, he sets forth five reasons why one skilled in the art could not have arrived at the presently claimed invention in 1998 based on

the teachings of Khwaja *et al.* in view of Schena *et al.* These five reasons can be summarized as follows:

- (1) Since the disclosures of Khwaja *et al.* and Schena *et al.* are in very disparate areas of science, someone working on botanical products would not have customarily been exposed to both papers;
- (2) Those working in the botanical field in the early 1990's followed a very descriptive and non scientific approach and would not, therefore, have been motivated to combine these teachings to arrive at the currently claimed invention;
- (3) As one skilled in the art, Dr. Theodorescu states that "it is not at all obvious that even in my lab we would have thought of this concept in 1998, the time this patent was filed";
- (4) "BotanicLab, the makers of PC-SPES, did not have the idea or vision to formulate a quality control process based on gene expression profile which could have prevented the lot to lot variability that plagued their product in 2000-2002"; and
- (5) Even when considered together, the teachings of Khwaja *et al.* and Schena *et al.* would not lead one skilled in the botanical arts to arrive at the invention claimed in the present patent application.

Furthermore in paragraph 6 of the his Declaration, Dr. Theodorescu discusses a publication that he co-authored in 2003 that hypothesizes using molecular fingerprinting to standardize botanical mixtures. This publication (*i.e.*, Bigler *et al.*, *Oncogene* 22:1261-1272 (2003)) is attached to his Declaration as Exhibit B. Dr. Theodorescu makes the following two statements in this paragraph:

"Thus, as mentioned above in paragraph 5, it is my belief that one of ordinary skill in the herbal medicine arts could not have arrived at the invention now claimed in the Yale application in 1998 based on the combined teachings of Khwaja *et al.* and Schena *et al.*"

“It is also my belief that the invention now claimed in the Yale patent application could have real utility for determining an advanced form of quality control for botanical extracts and provides an important advancement in the standardization of herbal compositions.”

To establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings; (2) there must be a reasonable expectation of success; and (3) the prior art references must teach or suggest all the claim limitations. M.P.E.P. § 706.02(j). The Examiner has failed to satisfy any one of these three criteria in this rejection in the instant application and has therefore failed to establish a *prima facie* case of obviousness. We will now address each of these three criteria and explain why the rejection is fatally flawed and should be withdrawn.

“Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.” M.P.E.P. § 2143.02 (citing case law as support). As discussed above, Dr. Theodorescu establishes that there is absolutely no explicit or implicit teaching, suggestion, or motivation in Schena *et al.* that would motivate one skilled in the art at the time of the present invention to utilize gene expression profiles in the bioactivity “fingerprints” disclosed by Khwaja *et al.*

As also discussed in his Declaration, Dr. Theodorescu states that the teachings of Khwaja *et al.* and Schena *et al.* “are in very disparate areas of science”. To rely upon a reference under Section 103, it must be analogous prior art. M.P.E.P. 2141.01(a). Here, the Examiner is impermissibly applying “prior art” that is nonanalogous in rejecting the presently pending claims under 35 U.S.C. § 103(a).

It is only by having knowledge of Applicants’ present invention that one of ordinary skill in the art could have arrived at the presently claimed invention by combining the prior art relied upon by the Examiner. As clearly set forth above and in Dr. Theodorescu’s Declaration, it would not have been obvious to one skilled in the art to combine the teachings of Khwaja *et al.*

and Schena *et al.* so as to arrive at the invention claimed in the present invention. Therefore, the Examiner's conclusion of obviousness is based on improper hindsight reasoning. M.P.E.P. § 2145 (Section X. Subsection A).

There was also no reasonable expectation of success if one were to combine the teachings of the two cited references at the time of the present invention in 1998. As discussed in his Declaration, Dr. Theodorescu explains that those of ordinary skill in the art, including his own lab as well as the makers of PC-SPES (*i.e.*, BotanicLab), did not solve the problem addressed by the presently claimed invention in spite of a great need to do so and the availability of the combined teachings of Khwaja *et al.* and Schena *et al.*

Also, as discussed both herein and in Dr. Theodorescu's Declaration, the prior art references relied upon by the Examiner fail to teach or suggest all the claim limitations of the presently pending claims. Again, Khwaja *et al.* fail to even mention gene expression, while Schena *et al.* fail to discuss utilizing gene expression profiles to standardize herbal compositions.

Dr. Theodorescu's Declaration also discusses how the presently claimed invention satisfies a long-felt need for a method of standardizing botanical compositions to improve their safety and efficacy as pharmaceuticals. See, for example, paragraph 5 of the Declaration describing the PC-SPES situation. His Declaration establishes that the present invention addresses an art recognized problem, that the long-felt need was not satisfied by another before Applicants' invention, and that the invention does in fact satisfy the long-felt need.

In summary, the Examiner has failed to establish a *prima facie* case of obviousness. The prior art relied upon by the Examiner provides no teaching, suggestion, or motivation to combine the prior art teachings so as to arrive at the presently claimed invention; there was no reasonable expectation of success based on the cited references; and the cited references do not teach or suggest all the limitations of the presently pending claims. The Examiner has clearly used impermissible hindsight to arrive at the obviousness rejection set forth in the Final Office Action. In view of Dr. Theodorescu's Declaration and the reasons cited herein, the Examiner is respectfully requested to withdraw this rejection and allow the presently pending claims. to go to issuance.

Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request reconsideration and the timely allowance of the pending claims. A favorable action is awaited. Should the Examiner find that an interview would be helpful to further prosecution of this application, he is invited to telephone the undersigned at his convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310. If a fee is required for an extension of time under 37 C.F.R. 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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Dated: March 16, 2005
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